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10/694,586	10/27/2003	Ekambar R. Kandimalla	HYB-005US5	3762

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EXAMINER	
HORNING, MICHELLE S	
ART UNIT	PAPER NUMBER
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,586	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20, 21, 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to communication filed 12/26/2007. The status of the claims is as follows: claims 20, 21 and 41 are both pending and under current examination and claims 1-19 and 22-40 are canceled.

The following rejection has been withdrawn due to claim amendments:

1. 35 USC 112, 2nd paragraph.

Claim Rejections - 35 USC § 103-MAINTAINED

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaix et al (1996) and US Patent # 6562798 (Schwartz). The claims were rejected because the applied prior art met the claim limitations as well as provided a

motivation to combine the teachings. Briefly, Chaix et al disclose oligonucleotides comprising a 3'-3' linker and two accessible 5' ends. The authors further disclose a marked increase in the oligonucleotides' stability in contrast to that of 5'-3' sequences. Separately, Schwartz discloses immunostimulatory oligonucleotide sequences comprising a CpG dinucleotide wherein the cytosine is modified. Based on these teachings, the Examiner concluded that it would have been obvious to one of ordinary skill in the art to combine the teachings above in order to make a CpG-containing sequence with modified cytosines as taught by Schwartz and further incorporate a 3'-3' linker as disclosed by Chaix et al. One would have been motivated to do so in order to increase the oligonucleotides' stability against nuclease-mediated degradation (see Chaix et al, last paragraph). Of note, Chaix et al teach that there is a marked increase in the structural integrity of an oligonucleotide by inserting a 3'-3' linker and this insertion would have been obvious for any oligonucleotide of *any function*. There would have been a reasonable expectation of success given that the success is well described in the prior art by both references and the underlying techniques are widely used. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill at the time the invention was made.

In response, Applicants submit that Chaix et al fails to teach or suggest an immunostimulatory oligonucleotide which specifically comprises a CpG dinucleotide wherein either or both of nucleotides may be modified or not at all. Secondly, Applicants state the following: "Schwartz et al. exclusively describes immunostimulatory sequences in which the C residue of a CG dinucleotide is modified". Also stated is the following:

"Schwartz provides no teaching or suggestion to further modify the oligonucleotide with an immunostimulatory moiety"; see Remarks on page 8. Lastly, Applicants submit that there is no motivation to combine the teachings to arrive at the claimed invention with any reasonable expectation of success.

Applicants' arguments have been considered but not found to be persuasive. The motivation to combine the teachings was clearly stated by the Examiner which is to increase the stability of the oligonucleotide by specifically incorporating a 3'-3' linker; Applicants have failed to respond to this motivation. While Chaix et al does not teach using sequences containing a CpG, this is considered irrelevant to the fact that the insertion of a 3'-3' increases the structural integrity of oligonucleotides possessing *any downstream function* in comparison to sequences in its 5'-3' orientation. Applicants also state that Schwartz et al discloses a CpG-containing oligonucleotide wherein the cytosine is modified; it is not clear what is meant by this statement. However, the Examiner would like to remind the Applicants that the claimed invention is also drawn to modified cytosines within a CpG dinucleotide (see claim 1) wherein the guanosine can either be modified or a natural purine nucleoside. Lastly, the Examiner maintains that there would be a reasonable expectation of success given the underlying techniques are widely used and taught successes by the applied prior art. While Applicants submit disapproval of this, no argument was presented.

Double Patenting-MAINTAINED

The following rejections are maintained because Applicants have decided to consider any actions deemed necessary at a later time. Further, other rejections are still pending.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-21 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/174448. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/234074. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/234075. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/174002. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/173983. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/173794. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/174282. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of

claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/173938. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/174450. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39 and 40 of copending Application No. 11/270805. Although the conflicting

claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20-21 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 10/757345. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20, 21 and 41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37, 39, 40 and 42-60 of U.S. Patent No. 7276489. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an oligonucleotide comprising a linker and two accessible 5' ends. Both sets of claims are drawn to 2'-deoxy-7-deazaguanosine.

Claim Rejections - 35 USC § 103-NEW

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 21 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaix et al (1996), US Patent # 6562798 (Schwartz), Smee et al (1991) and Schneider and Chait (1995). As discussed above, the combined teachings of Chaix et al and Schwartz meet the limitations of claims 20 and 21. Briefly, Chaix et al discloses that oligonucleotide sequences which include a 3'-3' linker and two accessible 5' ends demonstrate a marked increase in sequence stability. The teachings of Schwartz provide CpG containing sequences, in which the C is a modified cytosine. However, Chaix et al and Schwartz do not teach or suggest using 7-deazaguanosine (new claim 41 of the instant application).

Smee et al disclose the immunoenhancing properties as well as the antiviral activity of 7-deazaguanosine in mice (see whole document). The authors demonstrate that this active compound has antiviral activity in mice against a variety of RNA viruses but lacks antiviral properties in cell culture (see Introduction). Figure 2 reveals the induction of interferon following single inoculations. The authors describe this induction as rapid with high levels detected in the serum within 1 to 4 hours after administration (see Results, page 153). Further, NK cell activity was augmented in spleens following treatment with 7-deazaguanosine as depicted in Figure 3. The authors also note that 7-deazaguanosine is not toxic to mice (see Discussion, page 156).

In addition to the known immunoenhancing properties, Schneider and Chait teach that incorporation of a 7-deazaguanosine within nucleic acid sequences leads to

increased stability (see whole document). The use of matrix-assisted laser desorption mass spectrometry (MALDI-MS) is described by the authors to be limited in that there is a tendency for oligonucleotides to undergo facile fragmentation (see Abstract). The authors disclose that this tendency for fragmentation is greatly influenced by the chemical structure of the oligodeoxynucleotides and set out to identify a modification that would inhibit such fragmentation (see Introduction, page 1571). In conclusion, the authors determined that incorporation of either a 7-deazaguanosine or 7-deaza-adenine into DNA revealed a "significantly increased stability" compared to other 7-aza analogues under MALDI-MS conditions (see Conclusions, page 1574). Thus, the authors showed that incorporation of these other 1-aza analogues decreased the tendency for sequence fragmentation in comparison to guanine (see Conclusions, page 1574).

Thus, given the teachings above, it would have been obvious to one of ordinary skill in the art to make an immunostimulatory sequence comprising a 3'-3' linker and a CpG wherein the G is a 7-deazaguanosine. One would have motivated to do so in order to increase the stability of CpG-containing oligonucleotides. Incorporation of a 3'-3' linker or a 7-deazaguanosine has been shown to prevent nuclease-mediated degradation (Chaix et al) and fragmentation (Schneider and Chait). Further, the teachings of Smee et al reveal that 7-deazaguanosine is immunoenhancing and leads to the induction of interferon in mice. There would have been a reasonable expectation of success given the underlying techniques are widely known and commonly used. The

invention as whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/

Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648